REMARKS

Claims 2-3, 5-9 are pending in the subject application with claims 11-16 withdrawn from consideration. By this Amendment, applicants have amended claim 2. Support for the amendments to claim 2 can be found in Fig. 2. In addition, applicants have added new dependent claims 17-23. Support for new claims 17-23 can be found throughout the specification as filed. In addition, applicants have amended typographical errors in the Abstract. Applicants respectfully request entry of this Amendment. After entry of this Amendment, claims 2-3 and 5-9 will be pending in the subject application.

Abstract

The Examiner objected to the Abstract as having typographical errors.

In response, applicants have hereinabove amended the Abstract.

Claim Objections

The Examiner objected to claims 2 for typographical errors.

In response, applicants have hereinabove amended claim 2.

Claims Rejected Under 35 U.S.C. §103(a)

Claims 2,3 and 6-8

The Examiner rejected claims 2, 3 and 6-8 under 35 U.S.C. §103(a) as allegedly obvious over Ronai et al. *(Biochem. Biophys. Res. Comm.*, 1979, 91:1239-1249) in view of Abbruscato et al. (*J. Neurochem.*, 1997, 69:1236-1245) and Kanai et al. (*J. Biol. Chem.*, 1998, 273:23629-23632). The Examiner asserted that it would have been obvious to one of skill in the art, in light of Kanai et al., to, inter alia, (1) "substitute Met for Ala, to see what effect it would have on the analog potency and transport system" and (2) "modify the C-terminus of the peptide" and (3) "make a dimeric peptide analog of enkephalin."

In response, applicants respectfully traverse the Examiner's rejection. The modifications to the prior art proposed by the Examiner to somehow arrive at the claimed invention have unpredictable effects, and were known to be unpredictable by those skilled in the art at the time. Not only was the effect of *each* of the proposed modifications unpredictable, as indicated by the cited references, their *cumulative effect* is even less predictable. Applicants address the unpredictability of the Examiner's suggested modifications below:

(1) *"[S]ubstitute Met for Ala, to see what effect it would have on the analog potency and transport system"*

The December 28, 2007 Final Office Action appears to acknowledge that the effects of the proposed modifications were

unpredictable. The very wording of the rejection ("to see what effect") acknowledges the unpredictability of the proposed modification.

Furthermore, Kanai et al. teaches that the LTA1 transporter transports various amino acids *in preference* to methionine (see Fig. 2B, page 23631), thus teaching away from selecting methionine. The disclosure referred to by the Examiner discusses, in addition to methionine, the amino acids leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan and histidine. There is no rationale for selecting methionine from the group. In fact, the reference teaches away from the claimed invention because the inclusion of methionine is clearly *less* desirable than any of leucine, isoleucine, phenylalanine, or tryptophan. In regard to this, applicants draw the Examiner's attention to Fig. 2B of Kanai et al. which shows that all of these amino acids are transported at higher rates than methionine (see page 23631, Fig. 2B). The remaining references in combination with Kanai et al. do not cure these deficiencies.

(2) *"[M]odify the C-terminus of the peptide"*

The Examiner has suggested modifying the C-terminus based on Ronai et al. Applicants have previously noted that Ronai et al. teaches that any alteration of the C-terminus (of the peptides disclosed therein) "drastically" alters their binding ability (see, e.g., page 1245). The Examiner responded to this asserting that the statement by Ronai et al. "is not a negative implication. A 'drastic' alteration in the binding properties

can mean both 'increasing' and 'decreasing' the binding properties."

Applicants agree with the Examiner's characterization of the statement by Ronai et al. as meaning multiple things. Ronai et al., therefore, as well as the Examiner's acknowledgement, support the *unpredictability* of the effect of altering the C-terminus. Applicants further note, in specific regard to the Examiner's comment that Ronai's statement can mean both 'increasing' and 'decreasing' the binding properties, that "all imaginable responses" (i.e increasing or decreasing binding in this case) is not synonymous with "a predictable response." In fact the *opposite* results in different systems examined by Ronai et al. evidence the unpredictability of modifying the C-terminus (see summary of Ronai et al., p1239). The other cited references in combination with Ronai et al. do not cure these deficiencies.

Clearly, Ronai et al. illustrates the unpredictable nature of altering termini and altering residues where it notes differing and sometimes opposite effects in mouse vas deferens and guinea pig ileum (see paragraph starting on page 1241 and ending on page 1243). In addition, in view of this unpredictability, one of ordinary skill in the art, in light of the combination of Ronai et al., Kanai et al. and Abbruscato et al., would have no reasonable expectation of success of the claimed composition which possesses a considerable alteration of the C-terminus.

(3) *"[M]ake a dimeric peptide analog of enkephalin"*

There is no suggestion in the combination of cited prior art to make the claimed dimeric compounds of *specific* sequences, nor has the Examiner provided one. The Examiner alleged that there is a "reasonable expectation of success, since both Ronai and Abbruscato references teach enkephalin analogs that showed significant increase in potency." Applicants note that for the obviousness rejection to be proper there must be a reasonable expectation of success of the *claimed invention*, which recites specific sequences recited in claim 1, not of "enkephalin analogs" in general. This is especially significant in light of the differing effects of "enkephalin analogs" disclosed in Ronai et al. Applicnats have hereinabove noted the unpredictability of specific residue changes (e.g. C-terminus changes).

In addition, applicants note that Abbruscato et al. teaches away from those claimed dimeric compounds listed in claim 2 that do not contain phenyalanine (see page 1244, left hand column of Abbruscato et al. which teaches "significant decrease in the brain entry of [125Tyr1]biphalin" which they ascribe, in part, to the affinity of the large neutral amino acid carrier for the "two phenylalanine amino acids in the structure of this tandem enkephalin analogue"). Thus, the claimed dimeric compounds that do not contain phenyalanine would not be obvious from the cited references. In addition, there is no concept articulated by the Examiner, or cited in the prior art, how not having the two phenylalanine residues can somehow predictably result in an efficacious compound.

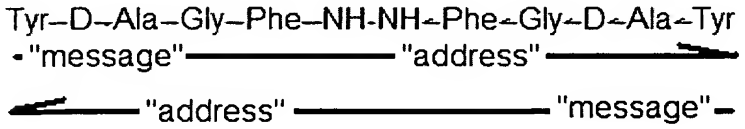
Unpredictability

Applicants note that opioid peptides comprise a "message" and "address" portion (see below).

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys
****message**** ========== address ==========

Message - address fragments in dynorphin

Modification in the "message" portion tends to influence potency of the analogue whereas modification in "address" portion mainly modulates receptor selectivity of the final compound. Biphalin and the dimeric peptides presented in the current application can be constructed by chemical tail-to-tail linking of the two identical opioid active fragments. From a structural point of view, the compound is built from two identical "message" and "address" elements. Thus, for the first N-terminal "message" part, the rest of molecule, including N-terminal fragment on the other side of hydrazide bridge plays "address" role.



A dimeric symmetric opioid peptide analogue is a double combination of messages and addresses

It should therefore be recognized that any single modification in the dimeric peptide results in modification of two amino acids in the whole molecule, e.g. replacement of D-Ala in position 2 of biphalin $(Tyr\text{-}D\text{-}Ala\text{-}Gly\text{-}Phe\text{-}NH\text{-})_2$ with D-Thr gives

peptide (Tyr-D-Thr-Gly-Phe-NH-)$_2$, in which two amino acid residues have been substituted, in the "message" portion of the peptide and *as well as* in the respective "address" fragments. The biological consequence of such double substitution is not predictable. Moreover, the peptide chain is so flexible that the secondary structure (which determines interaction with receptors and/or biological barrier carrier proteins) is not easily predictable.

Applicants maintain that the compound as claimed is not obvious over the combination of cited art. The multiple levels of unpredictability, not addressed by the Examiner in combining the cited references, teach against the obviousness of the invention. Applicants specifically note the importance of predictability as discussed in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. ___, 127 S.Ct. 1727 (2007) and the United States Patent and Trademark Office Examination Guidelines for Determining Obviousness as published in the Federal Register, Vol. 72, No. 195, October 10, 2007. Applicants maintain that the claimed invention is not obvious over the cited combination of prior art and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 2,3 and 5-9

The Examiner rejected claims 2, 3 and 5-9 under 35 U.S.C. §103(a) as allegedly obvious over Ronai et al. *(Biochem. Biophys. Res. Comm.*, 1979, 91:1239-1249) in view of Abbruscato et al. (*J. Neurochem.*, 1997, 69:1236-1245) and Kanai et al. (*J. Biol. Chem.*, 1998, 273:23629-23632) in further view of Hill et al. (U.S.

Patent No. 5,880,132), Bock et al. (EP 0434369) and Ornstein (U.S. Patent No. 5,356,902). The Examiner asserted that Ornstein, Hill and Bock et al. teach stimulatory amino acids, tachykinins and cholecystokinin receptor antagonists, and that Abbruscato et al. teaches biphalin, and that it would have been obvious to one of skill in the art to combine the teachings of the cited art to arrive at the invention as claimed.

In response, applicants respectfully traverse the Examiner's rejection. Applicants have stated hereinabove why the invention as claimed is not obvious over the combination of Ronai et al., Abbruscato et al., and Kanai et al. Applicants further note that the teachings of Hill et al., Bock et al. and Ornstein, in combination with the remaining cited art, do not cure these deficiencies. The combination of references does not teach or suggest $(Tyr\text{-}D\text{-}Met\text{-}Gly\text{-}Phe\text{-}NH\text{-})_2$, and does not teach or suggest applicants' invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

References Disclosed in International Search report

Applicants note that the present application is a §371 national stage of PCT International Application PCT/PL2003/00077. According to M.P.E.P §609.03, the Examiner has considered "the documents cited in the international search report in a PCT national stage application when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage file." The April 29, 2004 International Search Report issued in connection with the

above identified application (a courtesy copy of which is attached hereto as **Exhibit A**) cited two documents. Examiner has listed the first document, Lipkowski et al. (1999), Biorg. Med. Chem Let. 9:2763-2766, on the form PTO-892 which was attached to the March 5, 2007 Office Action. Applicants note that the second document, Lipkowski et al. (2002), 70(8):893-897, "Biological Properties of a New Fluorescent Biphalin Analogue," has not been listed in a PTO-892 by the Examiner. For completeness of the record, and in accordance with M.P.E.P §609, applicants attach hereto as **Exhibit B** a substitute form PTO-1449 listing Lipkowski et al. (2002), and respectfully request that the Examiner initial and return a copy of the form to the undersigned.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee, apart from the enclosed $60.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Gary J. Gershik 4/28/08
Gary J. Gershik Date
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EXHIBIT A

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
29 April 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BIPHALIN DERIVATES AND THEIR ANALGESIC APPLICATIONS

(57) Abstract: Application of peptides with analgesic properties as the active ingredient in devices for the direct application of medication to the site of their expected analgesic activity, particularly in the central nervous system.

WO 2004/014943 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL 03/00077

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/10 C07K14/70 A61K38/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A W LIPKOWSKI ET AL.: "Biological activity of fragments and analogues of the potent dimeric opioid peptide, biphalin." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, 1999, pages 2763-2766, XP004179967 OXFORD, GB ISSN: 0960-894X the whole document	1-16
X	A W LIPKOWSKI ET AL.: "Biological properties of a new fluorescent biphalin fragment analogue" LIFE SCIENCES., vol. 70, no. 8, February 2002 (2002-02), pages 893-897, XP002267427 PERGAMON PRESS, OXFORD, GB ISSN: 0024-3205 the whole document	1-16

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2004	13/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Masturzo, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]national application No.
PCT/PL 03/00077

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-16 are directed to a method of treatment of the human/animal11-16 body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

EXHIBIT B

Form PTO-1449 Substitute	U.S. Department of Commerce Patent and Trademark Office	Application Number	10/524,343
		Filing Date	January 30, 2006
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)		First Named Inventor	Andrzej Lipkowski et al.
		Art Unit	1654
		Examiner Name	Julie Ha
		Attorney Docket No.	73871/GJG/BJA

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Lipkowski, A. W. et al. (2002) "Biological properties of a new fluorescent biphalin fragment analogue." *Life Sciences*, Vol. 70, no. 8, pp. 893-897	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Applicants: Andrzej Lipkowski et al.
Serial No.: 10/524,343
Filed: January 30, 2006
Exhibit B